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Abnormal quantitative EEG scores identify patients with complicated idiopathic generalised epilepsy

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KEYWORDS
Idiopathic generalised epilepsy;
Quantitative EEG;
Personality disorder;
Pharmacoresistance

Summary *Objective*: To investigate the relationship between quantitative EEG (QEEG) scores and ''complicating factors'' (psychopathology, true pharmacoresistance, neurological symptoms) in idiopathic generalised epilepsy (IGE). *Methods*: 35 newly referred, newly diagnosed, unmedicated IGE patients were collected in a prospective and random manner. Standard neuro-psychiatric and EEG examination was done. The patients were treated and controlled at regular visits. After 2 years of follow-up, clinical data were summarised and were compared to QEEG results. Clinical target items were neurologic and psychiatric abnormalities, proven pharmacoresistance. Patients with at least one of these items were labelled ''complicated'', whereas patients without these additional handicap were labelled as ''uncomplicated''. The 12 QEEG target variables were: *Z*-transformed absolute power values for three (anterior, central, posterior) brain regions and four frequency bands (1.5—3.5; 3.5—7.5; 7.5—12.5; 12.5—25.0 Hz). QEEG scores outside the ± 2.5 *Z* range were accepted as abnormal. The overall QEEG result was classified as normal (0—2 abnormal scores), or pathological (3 or more abnormal scores). Clinical and QEEG results were correlated. *Results*: All patients with psychopathology showed 4—8 positive pathological scores (power excess not confined to a single cortical region or frequency band). The two patients with pure pharmacoresistance showed pathological negative values (delta power deficit) all over the scalp. Statistically significant ($P < 0.001$) association was found between patients with uncomplicated IGE and normal QEEG, and between complicated IGE and pathological QEEG. Patients with neurological items had normal QEEG. *Conclusion*: Higher degree of cortical dysfunction (as assessed in the clinical setting) is reflected by higher degree of QEEG abnormalities. QEEG analysis can differentiate between IGE patients with or without psychopathology. Forecasting psychopathology may be the practical application of the findings.

Introduction

Idiopathic generalised epilepsy (IGE) syndromes are overlapping electro-clinical entities. According to the definition elaborated by an ILAE Committee,

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''the patient usually has a normal interictal state, without neurologic and neuroradiologic signs''.[1] The majority of IGE patients can be successfully treated with standard antiepileptic drugs.[2] Diagnosis and treatment is not always easy, however, 15.5% of juvenile myoclonic epilepsy patients are resistant to antiepileptic drugs despite correct therapy and lifestyle.[3]About 25% of these patients has psychiatric and psychological problems that can counteract therapeutic efforts.[4,5] The negative impact of cognitive and personality disturbances on seizure control and quality of life has been confirmed repeatedly. Besides average intelligence, these young people are inclined to follow their momentary feelings and impulsions which results in instable, childish behaviour sometimes reaching the degree of levity. Planning their own future is often lacking because they are ''... more inclined to take things as they come than to act in accordance with an independent line of conduct'' as Janz wrote.[4] This sort of personality disturbance results in neglecting and dissimulating seizures, irregular intake of medication, ignoring proven seizure-provoking factors like sleep deprivation. In this way the patients are likely to suffer of self-provoked seizures and, in turn, self-perpetuated social maladjustment.[4,6–8] Neurological signs and abnormal radiological findings (in standard CT and MRI scans) may occur but have no impact on treatment and prognosis.[3,9] Focal features in IGE patients can hinder correct diagnosis, however.[10] Early recognition of these difficulties, in particular, psychopathology, can promote planning of effective treatment strategies.[6,8] The problem is that recognition of these complicating factors is not always easy. Neurological signs and mental retardation can be recognised at the first examination. In contrast, a peculiar personality trait that highly counteracts effective treatment[4] may be unrecognised at the first visit. Usually, analysis of recurrent therapeutic failures highlights that psychopathology is the cause of pseudoresistance. In cases of ''pseudoresistance'', the causes of persistent seizures are irregular intake of the drug and/or ignoring appropriate lifestyle by the patients. Also true pharmacoresistance cannot be diagnosed at the first visit.

Advanced neuroimaging studies and neuropathology revealed that the brain of IGE patients is not entirely normal in terms of structure and function.[11–16] Mild cortical pathology not detected by routine MRI probably contributes to neuro-psychiatric problems.[7,17] Interestingly, the percentage of IGE patients with psychiatric disturbances[4,5] is roughly equal to the percentage of IGE patients with significant cortical abnormalities detected by voxel-based MRI.[18] Some indirect evidence suggest that cortical pathology might contribute to pharmacoresistance, too.[3,19] In the light of these findings, it is reasonable to suppose that IGE patients with complicating factors have higher degree of cortical dysfunction than IGE patients without such additional handicaps. For several reasons, sophisticated neuroimaging can hardly be used as a routine screening method for cerebral abnormalities that are associated with psychopathology and pharmacoresistance. In contrast, quantitative EEG (QEEG) analysis is a proven tool to assess the degree and pattern of cortical dysfunction.[20,21] In a prior study we found that a group of IGE patients showed significant diffuse quantitative EEG alterations as compared to a healthy control group.[22] In that study we did not address the distribution of the QEEG abnormalities across the patients. Now we formulated and tested the hypotheses that (1) IGE patients do not have the same degree of QEEG abnormality, (2) higher degree of cortical dysfunction (as assessed in the clinical setting) might be reflected by higher degree of QEEG abnormalities.

Methods

The design of this study was approved by the Local Ethics Committee of the Institution. In a period of 2.5 years, all the newly referred patients who fulfilled inclusion criteria entered this investigation. Inclusion criteria were as follows: (1) newly diagnosed IGE (juvenile absence epilepsy, juvenile myoclonic epilepsy, epilepsy with generalised tonic-clonic seizures on awakening). The diagnosis was based on concordant clinical and EEG results.[1] Definition of the term ''newly diagnosed'' was a seizure history of 1 year or less. (2) No systemic or neuro-psychiatric illness except IGE. (3) No regular alcohol or drug use or misuse (contraceptives were allowed). (4) Freedom from any medications in the 5 days before EEG investigation. (5) Standard EEG record of good quality, according to recommendations for quantitative EEG studies.[23] Patients who had got generalised tonic-clonic seizures in the 3 days before EEG, or took any medication in the 5 days before EEG investigation, were excluded. All the patients were diagnosed, treated, and followed at the Outpatient Service of our Institution. History taking, routine neuro-psychiatric evaluation, conventional EEG evaluation were done at the first visit. Indications of cranial MRI were the presence of neurological items, and later, pharmacoresistance. Treatment with valproate was indicated in all the patients. No extra investigation

was done, no treatment was postponed or tapered off for study purposes. Patients were followed at regular visits. In case of therapeutic failure, potential causes were analysed. In difficult-to-treat cases other drugs (lamotrigine, ethosuximide) or combinations of these drugs were administered. In cases of personality disturbances and pseudoresistance, psychotherapy was indicated. Final evaluation of the patients was done after 2 years of follow-up. Based on the clinical data accumulated in this period, patients were classified as uncomplicated (no neurologic or mental problems interictally, responders to drugs), or complicated (any cerebral damage in the patient's history, neurological symptoms, psychiatric symptoms, personality disorder, pharmacoresistance). In this paper, the term ''personality disorder'' refers to the peculiar trait that is characteristic to IGE patients,[4] as described in the Introduction section of this paper. Part of this personality disturbance is neglecting and dissimulating seizures, irregular intake of medication, ignoring proven seizure-provoking factors. As a consequence, the patients are prone to self-perpetuated social maladjustment. This condition should be recognised in the clinical setting as soon as possible; psychological testing is not necessary.[4,6,8]

All the EEG recordings were done in the forenoon hours, in the same semi-isolated room, with the same equipment (Brain Quick BQ240) by trained personnel, according to recommended standards for quantitative EEG studies.[23] Silver–silver chloride electrodes were placed according to the 10–20 system, fixed by appropriate adhesive and conductive gel. Impedances did not exceed 5 kΩ. 19-channel EEG was recorded against a linked ears reference. In addition, two bipolar derivations were used to identify oculographic and myogenic artefacts. 12-bit on-line digitisation was used. Sampling frequency was 128 s^{-1}. Forty minutes EEG was recorded in the resting, eyes-closed condition. The patients[1] level of vigilance was verbally checked during the recording. EEG records were stored on optical disc. Off-line frequency analysis started with data file conversion to the format of the Neurometric Analysis System (NAS, Version 23.5). Sixty 2-s epochs reflecting relaxed–waking state of the subjects were selected for spectral analysis. Sample selection and analysis was done blindly, without knowing the patient's name and clinical data. Our standardised epoch selection protocol was used. Epoch inclusion criteria were: (1) presence of continuous physiological (''waking'' or ''resting'') alpha activity with alpha voltage maximum in posterior regions; (2) absence of artefacts, epileptiform or other nonstationary elements; (3) absence of patterns indicating drowsiness or arousal. After final visual revision of the edited epochs, they were submitted to Fast Fourier Transform (FFT). Leakage was reduced by Hanning window. Data of the 60 epochs were averaged. Absolute band power was computed for 19 monopolar derivations and four frequency bands (delta: 1.5–3.5 Hz, theta: 3.5–7.5 Hz, alpha: 7.5–12.5 Hz, beta: 12.5–25.0 Hz). NAS evaluated all neurometric parameters relative to its own normative database, using age-regression equations. Independent of age, sex and derivation, deviations of the individual values from the normative mean were expressed in *Z*-score.[24] In order to get regional spectral variables, electrode-related values were compressed by averaging. Delta, theta, alpha, beta power was computed for anterior region (ANT, composed of Fp1, Fp2, F3, F4, F7, F8, Fz values), central region (CENT, composed of T3, T4, C3, C4, Cz values), and posterior region (POST, composed of P3, P4, Pz, T5, T6, O1, O2 values).

Deviation of these 12 EEG variables from the mean ($Z = 0$) were evaluated in all the patients. Deviations of ($Z > \pm 2.5$) were scored as abnormal. The number and distribution of abnormal neurometric scores were compared in the patients with and without complicating factors.

Depending on the amount of abnormal scores, the QEEG finding was classified as ''normal QEEG'' (less than two abnormal scores), or, ''pathological QEEG'' (two or more abnormal scores). Binomial distributions were analysed by means of Fisher's exact test (GraphPad Prism 2.0). Differences with $P \leq 0.05$ were accepted as statistically significant.

Results

Thirty-five patients were investigated, treated and controlled (16 males, 19 females, age limits: 12–24 years, average: 17 years). Their clinical data are summarised in Table 1. Eleven patients were classified as complicated. Neurological items were found in three patients; their cranial MRI was within normal limits, however. Minor psychiatric disturbances were diagnosed in two patients (mild mental retardation and compulsive self-stimulation, respectively) at the first investigation. Personality disorder of the Janz type[4] was found in three patients who had juvenile myoclonic epilepsy. It was never identified at the initial investigation, but could be recognised at follow-up visits, within 2 years after the first visit. One patient displayed absence-like pseudoseizures in the course of the illness. Treatment was effective in 32 patients. Despite difficulties due to non-compliance, also two

Table 1 Clinical and quantitative EEG data of the patients.

Band	Clinical items	ANT	CENT	POST
Patient 1				
Delta		0.31088	0.847608	0.491416
Theta		1.424824	1.65845	0.016648
Alpha		1.929123	1.47067	1.001024
Beta		1.802924	1.265155	0.904999
Patient 2				
Delta	Right central facial palsy	−1.63885	−0.82875	−1.03608
Theta		0.377688	0.828789	0.524203
Alpha		0.763651	0.438586	0.205375
Beta		0.016373	0.089472	−0.03316
Patient 3				
Delta		0.012759	0.166161	−0.1496
Theta		1.481874	1.49589	1.556829
Alpha		0.944188	0.807005	0.425343
Beta		0.822654	0.512587	0.349063
Patient 4				
Delta	Mild mental retardation	**3.065305**	2.249343	1.729534
Theta		**4.286108**	**3.039844**	**2.625455**
Alpha		**3.228347**	**2.88906**	1.33583
Beta		**4.016199**	**2.51891**	1.786904
Patient 5				
Delta	Personality disorder	1.801816	**3.322929**	**2.595404**
Theta		**4.923313**	**4.620277**	**2.823014**
Alpha		**3.026751**	**2.727511**	1.438308
Beta		2.238273	1.822896	1.173346
Patient 6				
Delta		−0.0144	0.695721	0.792229
Theta		0.910841	0.6609	0.389974
Alpha		−0.44227	−0.18263	−0.18567
Beta		2.293835	1.086619	0.10202
Patient 7				
Delta		−0.65629	−0.39542	0.871796
Theta		0.015121	0.40871	1.008864
Alpha		1.300082	1.51135	1.028962
Beta		1.280231	1.195937	1.125488
Patient 8				
Delta	Personality disorder and pharmacoresistance	2.429249	2.278049	**4.02887**
Theta		**5.304621**	**4.446773**	**5.390082**
Alpha		**3.151268**	**2.576996**	2.080613
Beta		**3.512075**	2.422483	**2.736306**
Patient 9				
Delta		−0.92326	−0.91705	−0.5878
Theta		0.724819	0.349741	1.124451
Alpha		−0.1259	−0.34973	−0.15741
Beta		−0.27367	−0.79593	−0.78858
Patient 10				
Delta		−0.76201	−0.79149	−1.0714
Theta		−0.02919	0.105787	−0.50964
Alpha		0.844512	0.745494	0.386925
Beta		0.867955	0.332503	−0.27622

Table 1 (*Continued*)

Band	Clinical items	ANT	CENT	POST
Patient 11				
Delta		1.010249	0.819516	1.376778
Theta		**2.611484**	2.385491	1.844083
Alpha		2.161055	2.01015	1.441971
Beta		0.458882	0.389795	0.329511
Patient 12				
Delta	Pharmacoresistance	**−3.20185**	**−2.71718**	**−2.67932**
Theta		−1.50301	−0.90068	−1.67703
Alpha		−1.23073	−1.14346	−1.19992
Beta		−1.25992	−1.36071	−1.56627
Patient 13				
Delta		−1.03946	−0.57796	−0.64287
Theta		−0.21173	−0.22574	−0.24023
Alpha		0.314134	0.354242	0.272119
Beta		0.116182	0.050746	−0.17668
Patient 14				
Delta	Cerebral concussion in patient's history	**−2.5971**	−1.69692	−2.05564
Theta		−1.11202	−0.70517	−1.1994
Alpha		1.361125	0.192236	−0.50236
Beta		0.934795	0.778545	−0.10705
Patient 15				
Delta	Personality disorder	2.226824	2.412144	**2.901531**
Theta		**4.602868**	**4.471317**	**4.344932**
Alpha		2.140356	2.399588	1.517922
Beta		2.359571	1.997874	1.360339
Patient 16				
Delta		0.187624	0.246773	0.78972
Theta		0.805323	0.911677	1.421761
Alpha		2.354146	1.896885	1.781106
Beta		0.791241	0.89516	1.085975
Patient 17				
Delta		0.678467	1.276634	1.280058
Theta		1.885425	1.854698	1.767609
Alpha		2.039536	1.896808	1.519539
Beta		2.405804	2.136765	2.14372
Patient 18				
Delta		−1.52188	−0.86952	−0.93473
Theta		−0.74972	−0.52789	−0.88522
Alpha		1.036004	0.847684	0.8332
Beta		0.977996	0.686631	0.548921
Patient 19				
Delta		1.254199	1.429218	1.59811
Theta		**4.154491**	**3.807553**	2.410176
Alpha		**2.740311**	**3.005122**	1.925584
Beta		2.468215	2.30959	1.717678
Patient 20				
Delta		0.433856	0.485773	1.189957
Theta		1.544273	1.37124	1.232523
Alpha		2.234489	1.854433	1.371282
Beta		0.672631	0.455436	0.32823

Table 1 (*Continued*)

Band	Clinical items	ANT	CENT	POST
Patient 21				
Delta	Pharmacoresistance	**−3.23486**	**−3.05815**	**−2.93852**
Theta		−2.16056	−2.17171	−2.15926
Alpha		−1.97948	−1.85067	−1.73364
Beta		0.232642	−1.09746	−1.21954
Patient 22				
Delta		−1.5739	−1.57027	−1.73257
Theta		−0.30775	−0.43832	−0.80225
Alpha		1.582012	1.08266	0.356632
Beta		0.24162	−0.04525	−0.45494
Patient 23				
Delta		−0.89126	−0.05732	−0.11697
Theta		0.203397	0.532569	0.348521
Alpha		0.3083	0.385621	−0.2029
Beta		0.48674	0.506083	0.457137
Patient 24				
Delta		0.55479	1.085419	0.941792
Theta		2.279121	2.393341	1.572294
Alpha		0.694275	0.736635	0.168982
Beta		1.331664	1.056981	0.519622
Patient 25				
Delta		1.33401	1.598367	**2.673381**
Theta		2.277134	2.237014	**3.041324**
Alpha		1.863792	1.858197	2.192263
Beta		2.085814	2.149643	2.478859
Patient 26				
Delta		−2.14925	−0.67237	−0.94602
Theta		−0.44257	0.312179	0.000849
Alpha		1.219333	2.272273	1.081031
Beta		0.205117	0.780274	0.741893
Patient 27				
Delta	Self-induction of seizures	2.376185	1.996173	2.346125
Theta		**3.164408**	2.33983	**2.66294**
Alpha		**2.767684**	1.7987	2.04938
Beta		**3.311401**	2.041146	**2.795052**
Patient 28				
Delta	Perinatal hypoxya	−0.04489	0.325436	1.295653
Theta		−0.27276	−0.01253	0.727034
Alpha		2.24829	1.428922	1.882709
Beta		1.189696	0.98267	1.827979
Patient 29				
Delta		−1.75831	−1.37801	−1.48549
Theta		−0.39165	−0.79838	−1.07742
Alpha		0.036373	0.081404	−0.20156
Beta		−0.8614	−0.97133	−1.35139
Patient 30				
Delta		0.720329	1.607432	1.382499
Theta		2.05531	2.079673	1.776112
Alpha		2.18563	2.02664	1.539772
Beta		**3.634551**	2.490341	1.698804

Table 1 (*Continued*)

Band	Clinical items	ANT	CENT	POST
Patient 31				
Delta		−0.07772	0.39282	−0.10401
Theta		1.584289	1.59508	1.298563
Alpha		0.499498	1.091664	0.356403
Beta		0.599989	0.576474	−0.08987
Patient 32				
Delta		−0.66	0.761651	1.680449
Theta		0.127522	0.860599	0.970948
Alpha		1.440479	1.303	1.179837
Beta		0.60853	0.891097	0.750859
Patient 33				
Delta	Absence-like pseudoseizures	1.236846	1.02043	1.292326
Theta		**2.795835**	**3.350303**	**2.982875**
Alpha		1.839878	2.235002	1.408266
Beta		**3.614839**	**3.121821**	2.404069
Patient 34				
Delta		0.811427	1.142138	0.810987
Theta		2.361777	2.418365	2.104271
Alpha		2.033728	2.176713	1.464969
Beta		**2.964085**	2.461992	1.675566
Patient 35				
Delta		0.438445	0.521919	0.679708
Theta		2.388942	1.924981	1.802096
Alpha		1.039927	0.776619	0.824221
Beta		0.484722	0.140263	−0.16644

Z-transformed absolute power data for four frequency bands and three cortical regions (ANT: anterior, CENT: central, POST: posterior). Bold numerals indicate ($Z > \pm 2.5$) scores.

patients with personality disorder could be treated successfully. One patient with personality disorder and two patients without neuro-psychiatric items showed proven pharmacoresistance to valproate, lamotrigine, ethosuximide, and combinations.

Neurometric analysis and consecutive data compression resulted in 12 neurometric scores in each patient. The distribution of pathological scores across patients, cortical regions, and frequency bands is tabulated in Table 1. The results can be summarised as follows:

1. Clusters of positive abnormal values were found in all the patients with psychiatric items (patients no. 4, 5, 8, 15, 27, and 33). Abnormal scores did not show specific linkage to any cortical region or frequency band. Rather, they involved all cortical regions and 2−4 frequency bands.
2. Two patients with neurological items had completely normal scores, the third (patient no. 14) had a single abnormal one. This girl had a documented history of cerebral concussion, many years before the first absence seizure. However, no residual damage was present by neurological investigation and the recent cranial MRI was normal, too.
3. Patients with true pharmacoresistance but no neuro-psychiatric items (patients no. 12 and 21) showed selective involvement of the delta band: unusually low negative delta scores were found in all regions. Patient no. 18 with pharmacoresistance and psychopathology showed abnormal positive scores.
4. In the group of the uncomplicated IGE patients, 23/24 had normal QEEG. Out of them, 19 patients had not abnormal scores at all one, or two abnormal scores were found in 3 and 1 patients, respectively. Pathological QEEG (as defined above) was found in one uncomplicated patient (patient no. 19). The reason for this pathological QEEG finding remained hidden.
5. The comparison of the clinically uncomplicated and complicated groups showed that the former is associated with normal QEEG while the latter with abnormal QEEG (Table 2, $P < 0.001$).

Table 2 Relationship of clinical and QEEG findings (for definitions, see text).

	IGE patients		
	Complicated	Uncomplicated	All
Normal QEEG	3	23	26
Pathological QEEG	8	1	9
All	11	24	35

Chi-square test ($P < 0.001$).

Discussion

In this prospectively, randomly collected sample of newly diagnosed, unmedicated IGE patients, so-called complicating factors (neurological, psychiatric symptoms, pathological personality traits, true pharmacoresistance) were present in 11/35. Roughly the same proportion of patients with these complicating factors was reported by other authors.[3–5,19] We found that some sorts of psychopathology (personality disorder, pseudoseizures) were not recognised at the first clinical visit. Our impression was that psychological support contributed to effective treatment of our patients with psychopathology. Thus, we agree that these conditions should be recognised and managed as soon as possible.[4,8]

The QEEG method we used is simple and can be reproduced without difficulty. Standard data acquisition and sampling allow 80–90% reproducibility of the univariate QEEG variables.[24] This degree of reproducibility is roughly equal to test–retest variability of the same spectral parameters.[25] It was disclosed that one can rely on the normative means of the NAS database independent of race and geographical differences.[26]

Our results confirmed the hypotheses that (1) IGE patients do not have the same degree of QEEG-defined cortical dysfunction, and (2) higher degree of QEEG abnormality corresponds to higher degree of cortical dysfunction. All but one (23/24) uncomplicated IGE patients with lesser degree of cortical dysfunction (as presumed by clinical results) had normal QEEG. In contrast, one group of the patients with presumed higher degree of cortical dysfunction (all the patients with psychopathology and/or pharmacoresistance) had pathological QEEG. Our results indicate that QEEG may be a useful method in differentiating between IGE patients with and without psychopathology at the beginning of the illness. QEEG alterations are not specific, however. The pattern of the spectral alterations (in terms of topography and frequency band) cannot differentiate between patients with diverse psychopathology like personality disorder,[4] mental subnormality, or a tendency toward developing pseudoseizures or self-stimulation. Introduction of multivariate QEEG parameters might contribute to this issue.[24,26] An alternative possibility is that mild diffuse derangement of cortical functions may be a non-specific predisposition to a variety of psychopathological disturbances.[28]

The neurophysiological basis of the association between psychopathology and abnormal QEEG has not been clarified yet. Increased volume of cortical grey matter,[18] seemingly subtle developmental abnormalities[13] can indicate the presence of widespread anomalous neuronal connections in IGE patients. Altered networks can be the pathological basis of enhanced neuronal synchronisation,[27] and in turn, increased spectral power. According to another hypothesis, aspecific ''thalamocortical dysrhythmia'' governed by T-type Ca^{2+} channels may be common to a few neurological conditions including epilepsy.[29] Interestingly, valproate, a drug that blocks T-type Ca^{2+} channels[30] partly reversed pathological delta–theta power excess in IGE patients.[31]

In contrast to psychopathology, neurological items were not accompanied by abnormal QEEG. Pathological items in medical history and mild neurological signs do not necessarily indicate significant cortical dysfunction, however.

Both patients with pure pharmacoresistance showed the same unique finding, significant delta power decrease all over the scalp. This pattern of abnormal QEEG was not found in other IGE patients. The results of two patients cannot be managed as a proven scientific finding, however. In order to elaborate this issue, a long-term prospective study is underway.

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